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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/087,513	KANEKO ET AL.	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,15,19 and 21-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,15,19 and 21-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11-25-03; 12-04-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-04-03 has been entered. Claims 14, 15, 19 and 21-36 remain pending and are under consideration in the instant office action.

Claim Rejections - 35 USC § 112

The rejection regarding the phrase "introducing into a vector DNA or liposome a nucleic acid encoding an envelope..." has been withdrawn because the phrase can be found on pg 4, lines 14-15.

The rejection regarding support for APCs with adjuvant has been withdrawn because the phrase can be found on pg 4, lines 20-23.

I. Claims 21, 24 and 26-36 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The phrase "deletion of amino acids 297-329 in said variable loop" remains new matter (claims 21, 24, 26, 27, 30 and 34). The specification does not give any indication

that the deletion is an amino acid deletion and not a nucleic acid sequence deletion (pg 26, line 16). Nor is it readily apparent to one of skill in the art at the time of filing that the deletion is of amino acids. Applicants argue the variable loop of HIV was well known and as a result one of skill in the art would know the description of the 297-329 deletion referred to an amino acid sequence. Applicants supply Back et al. (1993), which describes the gp41 coding region and "explicitly describes that amino acids 297 to 329 are part of V3 (pg 3, lines 1-4 of arguments; pg 6900, Fig. 2, right side, of Back). Applicants argue the declaration by Dr. Srinivasan believes those of skill in the art at the time of filing would have recognized that the numbers 297-329 in the specification referred to amino acids and not nucleic acids. Applicants' arguments are not persuasive.

The specification refers to the "vv-ΔV3 mutant with the Δ297-329 deletion" that was constructed using PCR products (pg 26, line 16). Thus, at first glance it appears as though the deletion refers to nucleic acids because PCR products are nucleic acids. Even if at second glance, one of skill wanted to determine for certain what applicants meant "the Δ297-329 deletion", one of skill would not have been able to tell whether applicants intended to mean a deletion of amino acids 297-329 or nucleic acids 297-329. The specification does not state the Δ297-329 deletion is in the V3 loop or is amino acids. As written, the vv-ΔV3 mutant may have a mutation in the V3 loop and "Δ297-329 deletion" of nucleic acids 297-329. Thus, there was no way for one of skill in the art at the time of filing that the V3 loop of vv-ΔV3 was the "Δ297-329 deletion" or that the "Δ297-329 deletion" referred to amino acids 297-329.

Furthermore, applicants arguments are in error because Back taught the V3 loop was amino acids 299-330, not 297-329 as claimed (see pg 6900, Figure 2 and the amino acid numbers of PNNNTRKSIRIQRGPGRAFVTIGKIGNMRQAH). The mere reference to the V3 loop of HIV-1 III B by Back et al. does not support applicants' position. It is not readily apparent from Back et al. that the deletion described in the specification must be amino acids 297-329. Nor is it readily apparent that the deletion described in the specification refers to the HIV isolate described by Back et al. The arguments do not provide any reasoning as to why one of skill would have known that the numbers must have referred to amino acids and not to nucleic acids. Therefore, it would not have been readily apparent from the specification or the art at the time of filing to one of skill that "the Δ297-329 deletion" referred to amino acids as claimed.

II. Claims 14, 15, 19 and 21-36 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The claims require DNA encoding an envelope glycoprotein of HIV having a deletion of the third variable loop. The only DNA encoding an envelope glycoprotein of HIV having a deletion of the V3 loop described in the specification are vv-ΔV3 (pg 26, line 16), 1ΔV3, 7ΔV3 and 8ΔV3 (pg 34). The specification does not provide adequate

written description for one of skill to make vv-ΔV3 (pg 26, line 16), 1ΔV3, 7ΔV3 or 8ΔV3; therefore, the specification does not provide adequate written description for DNA encoding an envelope glycoprotein of HIV having a deletion of the V3 loop as claimed.

The specification does not provide adequate written description for vv-ΔV3. Kmieciak et al. (June 1, 1998, J. Immunol., Vol. 160, pg 5676-5683) teaches vv-ΔV3 was made using "the Δ297-329 deletion" taught by Wyatt (Dec. 1992, J. Virology, Vol. 66, pg 6997-7004). The Δ297-329 deletion of Wyatt was a deletion spanning the V3 loop, wherein Gly-Ala-Gly was inserted in place of the loop. Wyatt also taught the strain of HIV used to make the Δ297-329 deletion was HXBc2 (pg 6998, col. 1, 2nd para.). The specification does not teach the Δ297-329 deletion had Gly-Ala-Gly inserted in its place. The specification does not teach the starting material was HXBc2. In fact, the specification teaches the strain was HIVIIIB. Nor does the specification reference Wyatt. The specification does not teach the numbering of amino acids or nucleic acids and such number cannot be limited to the teachings of Kmieciak or Wyatt. As such, the specification does not provide adequate written description for one of skill to make vv-ΔV3.

Applicants state the method used to make 1ΔV3, 7ΔV3 and 8ΔV3 mutants was described in Kmieciak. Applicants summarize the method used to make 1ΔV3, 7ΔV3 and 8ΔV3 on pg 4-5 of response and ¶ 23 in the declaration by Dr. Srinivasan in ¶ 23. Applicants conclude that it is Dr. Srinivasan's opinion that those skilled in the art at the time of filing would have know that the vv-ΔV3 mutant with "the Δ297-329 deletion" was

a construct in which amino acids 297-329 of V3 were replaced with Gly-Ala-Gly (¶ bridging pg 5-6 of response).

Applicants' arguments are not persuasive. Kmieciak (June 1, 1998) was not available at the time of filing (5-29-98). Applicants summary of the method used to make 1ΔV3, 7ΔV3 and 8ΔV3 may be how 1ΔV3, 7ΔV3 and 8ΔV3 were made, but applicants do not in any way discuss how the method correlates to the specification as originally filed. Nor do applicants discuss how one of skill would have known how to make the starting material, vv-ΔV3 or how one of skill would have known from the specification as originally filed what deletions were performed to make 1ΔV3, 7ΔV3 and 8ΔV3. In this case, the conclusion in the paragraph bridging pg 5-6 is in error because it is not based on any scientific or logical reasoning or on the specification as originally filed.

Furthermore, the specification taught the starting material was HIV IIIB (pg 26, line 12), not HXBc2 as described by Wyatt. One of skill would not have known the Δ297-329 mutant described on pg 26, line 16 of the specification, had an insertion of three amino acids as described by Wyatt based on the description originally filed. Nowhere does the specification as originally filed imply that three amino acids were inserted. Nor does the specification imply that the Δ297-329 is limited to the vector described by Wyatt et al. in which three amino acids are inserted into the deletion. One of skill in the art at the time of filing would not have any way of knowing that the vv-ΔV3 mutant with the Δ297-329 deletion" described on pg 26, line 16, also had an insertion of Gly-Ala-Gly or was limited to the Δ297-329 mutant described by Wyatt et al.

While the specification disclosed the 1ΔV3, 7ΔV3 and 8ΔV3 mutants in Example 14 (page 34, Fig. 1), the specification does not teach how to make such mutants, how the mutants differ from each other, how the mutants differ from the vv-ΔV3 mutant with the Δ297-329 deletion (pg 26) or the structural elements of the mutants. The specification discloses the WTP-2, WTP-5 and WTP-8 (pg 35, line 3; pg 36, line 16; Fig. 1), but the specification as originally filed did not teach how the envelope gene in these vectors differed from each other or from the V3 mutants or how these vectors are "modified".

Claims 14 and 15 are directed toward a method of making a vaccine against HIV. Claim 19 is directed toward a method of making a vaccine that induces cellular immunity against HIV. Claim 28 is directed towards a method of stimulating a CTL response against HIV. Claims 32-36 are directed towards a method of stimulating a CTL response in a patient. The only disclosed purpose for vaccinating against HIV, inducing cellular immunity against HIV or stimulating a CTL response against HIV is to treat or prevent HIV infection (pg 1, line 12; pg 23, line 9). The specification does not provide adequate written description for any DNA encoding an envelope glycoprotein of HIV with a deletion in V3 capable of treating or preventing HIV, specifically capable of inducing a cellular immune response against HIV that is therapeutic or prophylactic.

The specification does not provide adequate written description for a method of making DNA encoding an HIV envelope glycoprotein having a deletion in the V3 loop or a cell expressing such an envelope glycoprotein that is capable for being used to treat or prevent HIV, specifically to induce a therapeutic or prophylactic cellular immune

response against HIV. The specification does not teach obtaining a cellular immune response that is directed toward HIV or obtaining a therapeutic or prophylactic effect against HIV using the DNA or cells as claimed. The art at the time of filing did not teach how to obtain such an effect using DNA encoding an HIV envelope protein having a deletion in the V 3 loop. Without such guidance, the specification does not provide adequate written description for the structure of any DNA encoding an envelope glycoprotein of HIV with a deletion in V3 having the function of treating or preventing HIV.

Applicants' arguments (pg 6, 1st full ¶) and the declaration by Dr. Srinivasan (¶ 26) state that, in the Dr.'s opinion, the specification provides a detailed description of making the nucleic acids and cells in claims 14, 15, 19 and 21-36, and how to use them to make a vaccine against HIV, induce cellular immunity against HIV, stimulate CTL activity as specified in those claims. Therefore, applicants conclude that the one skilled in the art at the time of filing would have been able make and use the nucleic acids and cells claimed as a vaccine, to induce cellular immunity against HIV, stimulate CTL activity against HIV as claimed using the teachings of the specification as originally filed. Applicants' arguments are not persuasive.

Applicants' conclusion is in error because it is not based on any scientific or logical reasoning or on the specification as originally filed. Applicants have not provided art at the time of filing that taught treating or preventing HIV using vectors. Applicants have not provided pre- or post-filing evidence indicating the teachings in the specification as originally filed were adequate to treat or prevent HIV. Therefore, the

specification as originally filed did not provide adequate written description for methods of making or using vectors for treating or preventing HIV.

III. Claims 14, 15, 19 and 21-36 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record.

The claims require DNA encoding an envelope glycoprotein of HIV having a deletion of the third variable loop. The only DNA disclosed in the specification having a deletion of the V3 loop as claimed are vv-ΔV3 (pg 26), 1ΔV3, 7ΔV3 and 8ΔV3 (pg 34). The specification does not enable one of skill to make the ΔV3 mutants disclosed in the specification.

The specification does not enable one of skill to make vv-ΔV3. Kmieciak et al. (June 1, 1998, J. Immunol., Vol. 160, pg 5676-5683) teaches vv-ΔV3 was made using "the Δ297-329 deletion" taught by Wyatt (Dec. 1992, J. Virology, Vol. 66, pg 6997-7004). The Δ297-329 deletion of Wyatt was a deletion spanning the V3 loop, wherein Gly-Ala-Gly was inserted in place of the loop. Wyatt also taught the strain of HIV used to make the Δ297-329 deletion was HXBc2 (pg 6998, col. 1, 2nd para.). The specification does not teach the Δ297-329 deletion had Gly-Ala-Gly inserted in its place. The specification does not teach the starting material was HXBc2. In fact, the specification teaches the strain was HIVIIIB. The specification does not reference

Wyatt. It is unclear if the numbers describe nucleic acids of the V3 loop or the HIV IIIB genome or amino acids of a particular strain of HIV. Reference to "the Δ297-329 deletion" did not have an art accepted meaning at the time the invention was made because different HIV strains had different envelope proteins, different amino acid lengths and sequences, and different nucleic acid sequences. As such, the specification does not enable one of skill to make vv-ΔV3. applicants have not addressed this portion of the rejection.

The specification does not enable one of skill to make 1ΔV3, 7ΔV3 or 8ΔV3. The specification discloses the 1ΔV3, 7ΔV3 or 8ΔV3 mutants in Example 14 (page 34, Fig. 1) but does not teach how to make such mutants, how the mutants differ from each other, how the mutants differ from the vv-ΔV3 mutant with the Δ297-329 deletion (page 26) or the structural elements of the mutants. The specification discloses the WTP-2, WTP-5 and WTP-8 (page 35, line 3; page 36, line 16; Fig. 1), but it is unclear how the envelope gene in these vectors differs from each other or from the V3 mutants or whether these vectors are considered "modified". Applicants have not addressed this portion of the rejection.

Claims 14 and 15 are directed toward a method of making a vaccine against HIV. Claim 19 is directed toward a method of making a vaccine that induces cellular immunity against HIV. Claim 28 is directed towards a method of stimulating a CTL response against HIV. Claims 32-36 are directed towards a method of stimulating a CTL response in a patient. The only disclosed purpose for vaccinating against HIV or inducing cellular immunity against HIV is to treat or prevent HIV infection (pg 1, line 12;

pg 23, line 9). The specification does not enable one of skill to use DNA encoding ΔV3 mutants to treat or prevent HIV.

At the time of filing, it was unpredictable whether a nucleic acid construct would have a therapeutic or prophylactic effect against HIV. Ross of record (September 1996, Human Gene Therapy, Vol. 7, pages 1781-1790) states a major technical impediment to gene transfer is the lack of ideal gene delivery systems including vectors, promoters and modes of delivery (page 1782, column 2, first full paragraph). These technical parameters are required to obtain efficient delivery and sustained expression of the gene (Verma of record, Sept. 18, 1997, Nature, Vol. 389, page 239-242; see page 239, 3rd column, line 10). The difficulties in sustaining expression of a gene cause unpredictability in obtaining a therapeutic or prophylactic effect in a patient (Ross, page 1789, column 1, first paragraph). Therefore, the parameters required to obtain a therapeutic effect using DNA were unpredictable at the time of filing.

Regarding vaccines, it was unpredictable how to obtain a therapeutic effect against a virus using a single antigenic stimulus as a vaccine. Haynes of record (1993, Science, Vol. 260, pages 1279-1286) teaches the classic approach to vaccine development involves exposing cells of the immune system to the proper antigenic stimulus which stimulates a beneficial immune response. The prior art presents few examples where a single antigenic stimulus, such as a small limited peptide or a whole protein is found to engender a therapeutic or protective immune response. The successful art-recognized immunogens used as vaccines are derived from whole killed or live attenuated pathogens, comprised of complex antigenic mixtures or comprised of

inactivated toxins. Many of these successes were achieved with a certain degree of luck, influenced by some particular peculiarity or aspect of a given pathogenic agent. Therefore, it was unpredictable how to obtain a therapeutic effect against a virus using a single antigen.

Specifically regarding HIV vaccines, Stricker of record (Medical Hypotheses, June 1997, Vol. 48, pages 527-9; see page 527, last paragraph through all of page 528) teaches that attempts to develop a vaccine against HIV have been unsuccessful. In fact, HIV infection has defied the creation of an effective vaccine or immunotherapeutic. Overall, a lack of understanding about cellular immunity against HIV, the sequence variability of HIV and the rapid replication of HIV, as disclosed by Bangham of record contribute the ineffectiveness of vaccines against HIV (Nov. 29, 1997, Lancet, Vol. 350, pages 1617-1621; page 1617, top of column 1). It is not known what renders an antigen capable of stimulating beneficial or protective CTL responses to HIV. Therefore, the art at the time of filing did not teach that the envelope glycoprotein of HIV could be used to induce a therapeutic cellular immune response against HIV. Thus, the parameters required to obtain a therapeutic cellular immune response against HIV was unpredictable at the time of filing.

The specification does not enable one of skill in the art to use DNA encoding ΔV3 mutants or a cell expressing ΔV3 mutants for treatment or prevention HIV. The specification does not teach obtaining a cellular immune response that is directed toward HIV, obtaining a therapeutic or prophylactic immune response against HIV using DNA encoding ΔV3 mutants, specifically obtaining a therapeutic or prophylactic cellular

immune response against HIV using DNA encoding ΔV3 mutants. The art at the time of filing did not teach how to obtain such an effect using DNA encoding ΔV3 mutants. Without such guidance, the specification does not enable one of skill in the art to use DNA encoding ΔV3 mutants to treat or prevent HIV.

Applicants' arguments (pg 6, 3rd full ¶) and the declaration by Dr. Srinivasan (¶ 26) state that, in the Dr.'s opinion, the specification provides adequate guidance for one of skill to make the nucleic acids and cells in claims 14, 15, 19 and 21-36, and how to use them to make a vaccine against HIV, induce cellular immunity against HIV, stimulate CTL activity as specified in those claims. Therefore, applicants conclude that the specification as originally filed enables one of skill to make and use the nucleic acids and cells claimed as a vaccine, to induce cellular immunity against HIV, stimulate CTL activity against HIV. Applicants' arguments are not persuasive.

Applicants' conclusion is in error because it is not based on any scientific or logical reasoning or on the specification as originally filed. Applicants have not provided art at the time of filing that taught treating or preventing HIV using vectors. Applicants have not provided pre- or post-filing evidence indicating the teachings in the specification as originally filed were adequate to treat or prevent HIV. Applicants have not addressed the unpredictability in the art or pointed to any reason why the teachings in the specification as originally filed overcome the unpredictability in the art. Therefore, the specification as originally filed did not enable making or using vectors for treating or preventing HIV.

Applicants argue Rowland-Jones (1999) provides post-filing evidence demonstrating the methods and procedures described in the specification were adequate to make and use products capable of treating or preventing HIV. Specifically, applicants argue Rowland-Jones taught HIV-specific CTL was an important goal in controlling viral levels during infection. Applicants argue Kiska (2002) supports ΔV3 mutants that produce a CTL response. Applicants' arguments are not persuasive. Rowland-Jones, Kiszka and Kmieciak were not available to one of skill in the art at the time of filing and do not teach treating or preventing HIV infection. Rowland-Jones, Kiszka and Kmieciak do not correlate to the invention originally disclosed in the instant application because they used different vectors. Applicants do not correlate the teachings in the specification as originally filed to the teachings of Rowland-Jones, Kiszka or Kmieciak. It is not readily apparent that the ΔV3 mutants described by Kiszka (pg 4223, col. 2, 1st full para.) correlate to the ΔV3 mutants described in the specification. The means by which ΔV3 mutants described by Kiszka induced a CTL response against gp160 *in vivo* is not described in the specification.

The specification provides CTL and antibody-dependent cell-mediated cytotoxicity data *in vitro* (page 35-38), but does not provide any examples of inducing cellular immunity against HIV *in vivo*. Nor does the specification provide adequate correlative evidence between *in vitro* data and *in vivo* results such that a therapeutic cellular immune response against HIV could be obtained *in vivo*.

The state of the art at the time of filing was that CTL assays *in vitro* produce variable results depending on the target cells used, the effector to target ratio used, and

the incubation time (Lancki of record, 1992, Biotherapy, Vol. 5, pages 71-81; see page 72, column 1, line 1) CTL assays combine PBL and target cells that are artificially "loaded" with antigen. The amount of antigen required on the target cell surface to induce a CTL response depends upon the immunostimulatory epitope of the antigen, the type of immune response and the strength of the immune response desired. Moreover, CTL assays do not account for the complex interaction of the immune response and cytokine regulation that occurs *in vivo*. For example, Bachmann of record reviews the use of the cellular immune response both *in vivo* and *in vitro* in viral assay systems (1994, Current Op. Immunol. Vol. 6, pages 320-326). A comparison of sensitivities shows that radioactive CTL assays are more sensitive than *in vivo* assays, but that results of secondary *in vitro* stimulation need to be verified by *in vivo* assay. On page 323, Bachmann states one should be very cautious not to 'over-interpret' results obtained by a cytolytic assay where cells are stimulated *in vitro* because the results may be biologically irrelevant without *in vivo* confirmation. Therefore, it was unpredictable at the time of filing whether a CTL response obtained *in vitro* could be obtained *in vivo* or that a cellular immune response obtained *in vivo* equivalent to the cellular immune response obtained *in vitro* will have any biological relevance.

The *in vitro* CTL and ADCC assays disclosed in the instant application require PBMC isolated from an HIV patient and autologous B-LCL or Jurkat cells transfected with the vectors of the invention as target cells which do not correlate to cells or nucleic acids used to treat viral infection *in vivo*. The specification does not teach the strain of HIV in the patients used to make the PBMC *in vitro*, the level of antigen expression on

the surface of target cells *in vitro*, the level of expression required *in vivo*, or how the immune response obtained *in vitro* correlates to response expected *in vivo*. It is not clear that the ratios of target to effector ratio used *in vitro* correlates to the ratio of transfected cells to effector cells that would occur *in vivo*. It addition, applicants activated the PBMC with antibodies which is an artificial means used to increase the activity of the cytotoxic cells and does not correlate to conditions found in the HIV patients because patients PBMCs are not stimulated with anti-CD3 antibodies. In addition, the specification does not teach that the level of cellular immunity *in vitro* would have any therapeutic benefit in a patient. Given the state of the art regarding the lack of correlation between *in vitro* and *in vivo* cytotoxicity taken with the guidance provided in the specification, it would have required one of skill undue experimentation to determine the parameters required to obtain an cellular immune response *in vivo* that has a therapeutic or prophylactic effect.

Claims 14, 15, 19, 21, 23, 24, 28-30, 32-34 and 36 encompass modifying the envelope glycoprotein of any strain of HIV. The state of the art at the time of filing was such that the V3 region of HIV varied between HIV strains and mutated frequently (page 1, line 15; page 2, line 13; page 3, line 3). The specification only teaches modifying the V3 loop of the HIV-IIIB envelope glycoprotein (page 26, line 12). The specification does not teach how to modify the V3 loop of the envelope glycoprotein of any other strain of HIV or correlate the V3 loop of HIV-IIIB to other strains of HIV such that similar modifications could be made or that a therapeutic cellular immune response could be

induced against the glycoprotein. Applicants have not addressed this portion of the rejection.

Applicants demonstrate different modifications of HIV-IIIB cause different effects (e.g. 1 V3, 7 V3 or 8 V3 mutants induce different immune responses, Fig. 1). Therefore, the specification does not enable one of skill to determine how to modify the V3 loop of any HIV envelope glycoprotein such that a therapeutic cellular immune response against HIV is obtained. Applicants have not addressed this portion of the rejection.

IV. Claims 21, 24, 26-36 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons of record.

It is unclear from the specification that the deletion of the V3 loop is of amino acids 297-329 as claimed and not of nucleotides 297-329 in the DNA. Applicants' arguments are addressed above in the new matter, written description and enablement rejections above.

Claims 28-36 are indefinite because the phrase "introducing into a vector DNA or liposome a nucleic acid encoding an envelope..." is grammatically unclear. A nucleic acid does not encode anything because it a molecule; a nucleic acid sequence encodes an envelope protein. The metes and bounds of how a nucleic acid is "introduced" into "vector DNA" or a "liposome" are unclear. Use of the phrase "vector DNA" is unclear because it does not have an art established meaning and cannot be found in the specification. Putting a nucleic acid into a vector is a completely different process than

putting a nucleic acid into a liposome carrier; therefore, combining the two concepts into one step is confusing. Applicants' arguments relate to Dr. Srinivasan's opinion, to what the phrase was intended to mean and to the definition of "vector DNA". Applicants' arguments are not persuasive. The arguments do not address the remarks by the examiner or provide any reasoning why the phrase must be interpreted as applicants' alleged intended meaning. In addition, pg 9, lines 20-21, defines a vector, not "vector DNA" as claimed.

Claims 29 and 33 are indefinite because it is unclear whether the "adjuvant" in claim 29 is the adjuvant of claim 28 or a different adjuvant. Applicants' arguments relate to Dr. Srinivasan's opinion as to how the claims would be interpreted to one of skill in the art. Applicants' argument is not persuasive. The arguments do not address why the adjuvant "could be both the same as or different from the adjuvant specified in Claim 28" and is not limited only to the adjuvant in parent claim 28.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at 571-272-0738.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER